Remarks

Reconsideration of this Application is respectfully requested.

Claims 4, 8 and 13 are sought to be amended. Support for the amendment to claim 4 can be found, *inter alia*, in the specification at page 20, lines 14-16. Claim 8 was amended for grammatical purposes and claim 13 was amended merely to reflect proper claim dependency.

Upon entry of the foregoing amendment, claims 1-14 are pending in the application, with claims 1 and 2 being the independent claims. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Priority

The Examiner indicated that a translation of the foreign applications should be submitted under 37 C.F.R. § 1.55 should Applicants desire to obtain the benefit of foreign priority under 35 U.S.C. § 119(a)-(d) prior to declaration of an interference. (*See* Paper No. 7, page 2, ¶2.)

In compliance with the Examiner's request, Applicants submit herewith English translations of Argentine Application No. P98 01 05609, filed November 6, 1998 and

Argentine Application No. P99 01 00679, filed February 23, 1999, as well as statements that the translations of the applications are accurate.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 2 and 4 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. (*See* Paper No. 7, page 2, ¶3a.) In particular, it is the Examiner's position that

> [i]t is apparent that the host cell with the Accession number DSM ACC2397 is required to practice the claimed invention. As such the host cell must be readily available or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If the host cell is not so obtainable or available, the requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the host cell. . . . If a deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants . . . stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

(Paper No. 7, pages 2-3, ¶ 3a.)

Applicants submit that host cell MC2 20 22/12/98 is readily obtainable by a repeatable method as set forth in the specification. (*See, e.g.*, page 16, line 24 to page 23, line 26.) In addition, Applicants note that the host cell MC2 20 22/12/98 was deposited under the terms of the Budapest Treaty (and given accession number DSM ACC2397) and submit herewith a Statement Concerning the Deposited Host Cell which provides that all restrictions on the availability to the public of the deposited host cell will be irrevocably

removed upon the granting of a patent. As such, Applicants request that the rejection of claim 2 under 35 U.S.C. § 112, first paragraph, be withdrawn.

With respect to claim 4, the Examiner asserted that the claim

> recites ". . . wherein said vector comprises pVex 1 . . .", however, "pVex1" is not an art recognized vector. All of the vectors disclosed on page 12, lines 11-14 of the instant specification are art recognized, except for "pVex1". Instant specification does not provide a description of the type of plasmid "pVex1" is or how to obtain this vector. Therefore since the "pVex1" recited in claim 4 is not described in the instant specification and since it is not art recognized and unavailable, one of ordinary skill in the art would not be able to practice the invention of claim 4. Appropriate correction is required.

(Paper No. 7, pages 3-4, ¶3b.)

Applicants note that the specification does describe the pVex 1 vector as well as a repeatable method on how to obtain it. (*See* Specification, page 12, lines 18-21 and page 19, line 26 to page 20, line 13.) Further, the pVex 1 vector was deposited under the terms of the Budapest Treaty on April 16, 1999 at DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Mascheroder Weg 1b, D-38124 Braunschweig, Germany, and was given accession number DSM 12776.

Applicants note that claim 4 has been amended to include the accession number of the pVex 1 deposit. Moreover, a Statement Concerning the Deposited Vector is submitted herewith which provides that deposited vector pVex 1 will be irrevocably and without restriction released to the public upon the issuance of a patent. Accordingly, Applicants submit that claim 4 complies with the requirements of 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1, 3 and 5-12 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lin, U.S. Patent No. 5,618,698 (hereinafter "Lin") in view of Powell, U.S. Patent No. 5,688, 679 (hereinafter "Powell"). (*See* Paper No. 7, page 5, ¶4a.) In particular, it is the Examiner's position that

> Lin teaches a host cell (COS, CHO cells), that is transected with a vector that comprises a nucleotide sequence encoding human erythropoietin (EPO), SV40 promoter and terminator, said host cell which further comprises pDHFR vector . . . . However, Lin does not disclose a host cell comprising a vector which comprises a nucleotide sequence which encodes the polypeptide consisting of the amino acid sequence set forth in SEQ ID NO:1 as recited in the claims.

(Paper No. 7, page 5, ¶4a.)

The Examiner further described Powell as teaching

> a host cell which comprises nucleotide sequence which consists of a 2.4 kb ApaI restriction fragment of genomic human ertyhropoietin [sic] . . . . Powell teaches that ApaI restriction fragment of the human ertyhropoietin [sic] gene was selected to maximize efficient transcription of ertyhropoietin [sic] RNA and effective translation and post-translation of the RNA into mature biologically active ertyhropoietin [sic] protein . . . .

(Paper No. 7, page 5, ¶4a.)

In view of the teachings of Lin and Powell, the Examiner concluded that

> it would have been obvious to one of ordinary skill in the art . . . to modify the host cell taught by Lin, by transfecting it with a nucleotide sequence encoding the mature form of erythropoietin, because Powell teaches that using a fragment of erythropoietin gene which encodes only the mature protein yields large amounts of biologically active mature protein.

(Paper No. 7, pages 5-6, ¶4a.) Applicants respectfully disagree with the Examiner's conclusions and traverse this rejection.

In order to make a prima facie case of obviousness, the Examiner must satisfy three basic criteria. First, there must be some suggestion or motivation, either in the references cited by the Examiner or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings to obtain Applicants' invention. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Second, there must be a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991.) Third, all the claim limitations must be taught or suggested by the prior art references. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). The suggestion to make the claimed combination, as well as the reasonable expectation of success, must be found in the prior art references, not in Applicants' disclosure. *In re Vaeck*, 947 F.2d at 491, 20 USPQ2d at 1442 (Fed. Cir. 1991.)

Applicants assert that there is no suggestion or motivation in Lin or Powell to combine the teachings to obtain Applicants' invention. Moreover, even assuming, *arguendo*, that such a suggestion or motivation to combine the references is present, there would be no expectation of success and all of the claim limitations are not taught or suggested by the references.

As acknowledged by the Examiner, Lin does not teach the claimed invention. (*See* Paper No. 7, page 5, ¶ 4a.) Applicants submit that Powell fails to remedy the deficiencies of Lin, in failing to suggest the claimed host cell comprising a vector which comprises a nucleotide sequence encoding the erythropoietin polypeptide consisting of the amino acid sequence in SEQ ID NO:1, a viral promoter and a viral terminator.

Powell discloses that including a nucleotide sequence in a host cell which consists of a 2.4 Kb ApaI restriction fragment of the genomic human erythropoietin gene maximizes

the transcription of erythropoietin RNA and the translation and post-translation of the RNA into mature biologically active erythropoietin protein. *See, e.g.,* Powell at col. 1, lines 57-67. Powell bases this purported discovery on the fact that the non-codifying fragments included in the ApaI fragment are critical for the observed effects. *See, e.g.,* Powell at col. 2, lines 14-35.

In contrast to the disclosure of Powell, the present invention does not employ an ApaI restriction fragment. Rather, the present invention is directed to a host cell comprising a vector which comprises a nucleotide sequence which only encodes the erythropoietin polypeptide consisting of the amino acid sequence in SEQ ID NO:1. That is, Applicants employ the erythropoietin gene itself, *i.e.,* the sequence included between the first ATG codifying codon for human erythropoietin and the stop codon of this same gene. The claimed nucleotide sequence of the present invention does not include any of the non-codifying sequences which, according to Powell, must be included in order to achieve high levels of expression.

The fact that the nucleotide sequence of the present invention does not include non-coding regions is a relevant difference between the present invention and the disclosure of Powell, since the purported inventive aspect of Powell is based on the presence of these non-codifying fragments. Powell emphasizes that the non-codifying sequences are critical for the high levels of expression, while the present invention, unexpectedly, shows this is not true.

Moreover, Powell employs an extremely complex construct in order to achieve elevated levels of productivity which comprises 350 bp of the adenovirus left-terminus, the origin and enhancer sequences from SV-40, the adenovirus major late promoter, the

adenovirus-2 tripartite leader and third leader 5' splice site, an immunoglobulin 3' splice site, and the late SV-40 polyadenylation signal in the EcoRI restriction site of pML. *See* Powell, col. 4, lines 36-44. In contrast to the disclosure of Powell, the present invention does not utilize such complex constructs. The vector constructs of the present invention are dramatically more simple than the ones which, according to Powell, are necessary for the achievement of the production of significant levels of erythropoietin. This simplicity allows for a greater facility in the handling of the genetic constructions, a higher theoretical stability of the constructions, and an easier means of controlling the genetic sequences employed for the production of erythropoietin.

In view of the above, it is evident that the present invention in nonobvious over Lin and Powell. The references clearly fail to teach or suggest a host cell comprising a vector which comprises a nucleotide sequence which only encodes the erythropoietin polypeptide consisting of the amino acid sequence in SEQ ID NO:1, a viral promoter and a viral terminator. In addition, in view of the fact that Powell discloses that non-coding regions of the erythropoietin gene and the use of complex promoters are necessary to generate high levels of the protein, one skilled in the art would be lead away from the teaching of the present invention. *See W. L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983) (error to find obviousness where references "diverge from and teach away from the invention at hand"). Accordingly, it is respectfully requested that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Objection to the Claims

The Examiner objected to claims 13 and 14 as being dependent upon a rejected base claim, but indicated that these claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. (*See* Paper No. 7, page 6, ¶5.) Based on Applicants' arguments in response to the 35 U.S.C. § 103(a) rejection, Applicants submit that claims 13 and 14 are dependent upon allowable claims. As such, the basis for the objection has been rendered moot, and Applicants respectfully request that the objection to the claims be withdrawn.

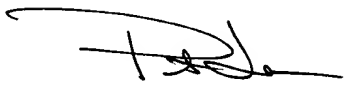
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Peter A. Jackman
Attorney for Applicants
Registration No. 45,986

Date: Nov. 17, 2003

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600